Form PTO-1390 P22119.P01	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER P22119
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 CFR 1 5) 10/070435

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/06399	20 September 2000	20 September 1999

TITLE OF INVENTION

METHOD FOR PRODUCING CYCLIC LACTIC ACID OLIGOMER

APPLICANT(S) FOR DO/EO/US

Mikio WATANABE, Jiro TAKANO, Yoshimi ISHIHARA and Masahiro MURAKAMI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. X This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ___ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U S C. 371.
3. X This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f))
4. X The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. X A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. X is attached hereto (required only if not communicated by the International Bureau).
   b. X has been communicated by the International Bureau
   c. ___ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. X An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
7. X Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C 371(c)(3))
   a. ___ are attached hereto (required only if not communicated by the International Bureau)
   b. ___ have been communicated by the International Bureau.
   c. ___ have not been made; however, the time limit for making such amendments has NOT expired
   d. X have not been made and will not be made
8. ___ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3))
9. X An oath or declaration of the inventor(s) (35 U.S.C. .371(c)(4)).
   "UNEXECUTED"
10. X An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (U.S.C. 371(c)(5)).

Items 11 to 16 below concern other document(s) or information included:

11. Assignee: AMATO PHARMACEUTICAL PRODUCTS, LTD., of Kyoto, JAPAN
12. ___ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
13. ___ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included
14. X A FIRST preliminary amendment.
    ___ A SECOND or SUBSEQUENT preliminary amendment
15. ___ A substitute specification
16. ___ A change of power of attorney and/or address letter.
17. X Figure of Drawing to be published_1_
18. X Other items or information:

    International Application as published in Japanese
    Cover Letter under 35 U.S.C 371 AND 37 C.F.R. 1.495
    PCT/IPEA/409 International Preliminary Examination Report.
    PCT/ISA/210 (in English & Japanese).
    PCT/IB/301.
    PCT/IB/304
    PCT/IB/308.
    PCT/IB/332
    PCT/IB/338
    PCT/IPEA/408 Written Opinion
    PCT/IB/306.
    PCT/RO/101 PCT REQUEST (with International Application as filed in Japanese).
    Claim of Priority

U.S. APPLICATION NO (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/070435	PCT/JP00/06399	P22119

19. X The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1 492(a)(1)-(5)).		
Search report has been prepared by the EPO or JPO. . . . . $ 890 00		
International preliminary examination fee paid to USPTO (37 CFR 1.482). . $ 710.00		
No international preliminary examination fee paid to USPTO (37 CFR 1 482) but international search fee paid to USPTO(37 CFR 1 445(a)(2). . . . . $ 740.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO. $1,040.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4). . . . . $ 100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of $130 00 for furnishing the oath or declaration later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 0 00	

Claims	Number Filed		Number Extra	RATE		
Total Claims	12	- 20 =	0	X $18 00	$ 0 00	
Independent Claims	1	- 3 =	0	X $84.00	$ 0.00	
Multiple dependent claim(s) (if applicable)				+ $280.00	$ 0 00	
TOTAL OF ABOVE CALCULATIONS =					$890.00	
___ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.					$ 0.00	
SUBTOTAL =					890.00	
Processing fee of $130 00 for furnishing the English translation later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +					0.00	
Extension of Time fee in the amount of $					0.00	
TOTAL NATIONAL FEE =					890 00	
Fee for recording the enclosed assignment (37 CFR 1 21(h) The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +					0 00	
TOTAL FEES ENCLOSED =					890.00	
					Amount to be refunded	$
					Charged	$

a. X A check in the amount of $890 00 to cover the above fees is enclosed.

b. ___ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees.

c. X The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0089.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO **CUSTOMER NO. 7055**
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Bruce H Bernstein
NAME

29,027
REGISTRATION NUMBER

Mar 19, 2002

P22119

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : M. WATANABE et al.

Appl. No :Not Yet Assigned
(U.S. National Phase of PCT/JP00/06399)

I.A.Filed: 20 September 2000

For : METHOD FOR PRODUCING CYCLIC LACTIC ACID OLIGOMER

COVER LETTER ACCOMPANYING U.S. NATIONAL STAGE PATENT APPLICATION FILED UNDER 35 U.S.C. 371 AND 37 C.F.R. 1.495

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Enclosed is a new National Stage patent application for filing in the U.S. Patent and Trademark Office under 35 U.S.C. 371 and 37 C.F.R. 1.495. The Declaration and Power of Attorney attached thereto are in unexecuted form. A properly executed Declaration and Power of Attorney will be filed within the period of time set in a Notification to be mailed by the United States Patent and Trademark Office.

Related to this, a correspondence address is provided in the unexecuted Declaration and Power of Attorney, and is as follows:

GREENBLUM & BERNSTEIN, P.L.C.
1941 Roland Clarke Place
Reston, Va. 20191

If there any questions pertaining to this National Stage Application, please contact the undersigned.

Respectfully submitted,
M. WATANABE et al.

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Reg. No. 31,096

March 19, 2002
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P22119.A01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Mikio WATANABE et al.

Serial No : Not Yet Assigned (National Stage of PCT/JP00/006399)

Filed : Concurrently Herewith (International Filing Date 20 September 2000)

For : METHOD FOR PRODUCING CYCLIC LACTIC ACID OLIGOMER

PRELIMINARY AMENDMENT

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to calculation of the filing fees and the examination of the above-identified patent application on the merits, the Examiner is respectfully requested to amend the claims as follows:

IN THE CLAIMS

Please amend claims 3-6 and 9-11, as follows (a marked-up copy of the amendment is provided in the attached Appendix):

3. (Amended) The method for producing a cyclic lactic acid oligomer according to claim 1, wherein in the first heating process (i), lactic acids are subjected to dehydration condensation reaction by heating to a temperature ranging from 120°C to 140°C under a pressure of 350 to 400mmHg.

4. (Amended). The method for producing a cyclic lactic acid oligomer according to claim 1, wherein in the second heating process (ii), the reaction product from the first heating process is heated to 145°C or higher, the reaction pressure is reduced to 100mmHg or lower at a depressurization rate of 0.5 to 1 mmHg/min, and the reaction is further continued under the reduced pressure and at a temperature of 145°C or higher so as to generate a dehydrated condensate of lactic acid.

5. (Amended) The method for producing a cyclic lactic acid oligomer according to claim 1, wherein in the second heating process (ii), the reaction product from the first heating process is heated to 150°C to 160°C, and while the reaction pressure is reduced to 15 to 20mmHg at a depressurization rate of 0.5 to 1mmHg/min, by-product water is removed by distillation while avoiding distillation of lactides, and after the reaction pressure is reduced to 15 to 20mmHg, the reaction is further continued under the same pressure and at a reaction temperature of 150°C to 160°C so as to generate a dehydrated condensate of lactic acid.

6. (Amended) The method for producing a cyclic lactic acid oligomer according to claim 1, which further comprises:
(iii) a third heating process for generating a cyclic lactic acid oligomer, which comprises a cyclization of a chain lactic acid oligomer in the reaction product from said second heating process by heating under a pressure lower than that of said second heating process.

9. (Amended) The method for producing a cyclic lactic acid oligomer according to claim 1, wherein cyclic lactic acid oligomers are selectively produced while substantially no chain lactic acid oligomers are produced.

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10. (Amended) The method for producing a cyclic lactic acid oligomer according to claim 1, wherein the ratio of cyclic lactic acid oligomers to total lactic acid oligomers in the reaction product is 80% by weight or more.

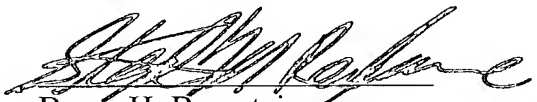
11. (Amended) A cyclic lactic acid oligomer produced by the method for producing a cyclic lactic acid oligomer according to claim 1.

REMARKS

By the above amendment, claims 3-6 and 9-11 have been amended to delete multiple dependency.

If there should be any questions, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,
Mikio WATANABE et al.



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APPENDIX
MARKED-UP COPY OF CLAIM AMENDMENTS

3. (Amended) The method for producing a cyclic lactic acid oligomer according to [claim 1 or 2] claim 1, wherein in the first heating process (i), lactic acids are subjected to dehydration condensation reaction by heating to a temperature ranging from 120°C to 140°C under a pressure of 350 to 400mmHg.

4. (Amended) The method for producing a cyclic lactic acid oligomer according to [any one of claims 1 to 3] claim 1, wherein in the second heating process (ii), the reaction product from the first heating process is heated to 145°C or higher, the reaction pressure is reduced to 100mmHg or lower at a depressurization rate of 0.5 to 1 mmHg/min, and the reaction is further continued under the reduced pressure and at a temperature of 145°C or higher so as to generate a dehydrated condensate of lactic acid.

5. (Amended) The method for producing a cyclic lactic acid oligomer according to [any one of claims 1 to 4] claim 1, wherein in the second heating process (ii), the reaction product from the first heating process is heated to 150°C to 160°C, and while the reaction pressure is reduced to 15 to 20mmHg at a depressurization rate of 0.5 to to 1mmHg/min, by-product water is removed by distillation while avoiding distillation of lactides, and after the reaction pressure is reduced to 15 to 20mmHg, the reaction is further continued under the same pressure and at a reaction temperature of 150°C to 160°C so as to generate a dehydrated condensate of lactic acid.

6. (Amended) The method for producing a cyclic lactic acid oligomer according to [any one of claims 1 to 5] claim 1, which further comprises:
(iii) a third heating process for generating a cyclic lactic acid oligomer, which comprises a cyclization of a chain lactic acid oligomer in the reaction product from said second heating process by heating under a pressure lower than that of said second heating process.

9. (Amended) The method for producing a cyclic lactic acid oligomer according to [any one of claims 1 to 8] claim 1, wherein cyclic lactic acid oligomers are selectively produced while substantially no chain lactic acid oligomers are produced.

10. (Amended) The method for producing a cyclic lactic acid oligomer according to [any one of claims 1 to 9] claim 1, wherein the ratio of cyclic lactic acid oligomers to total lactic acid oligomers in the reaction product is 80% by weight or more.

11. (Amended) A cyclic lactic acid oligomer produced by the method for producing a cyclic lactic acid oligomer according to [any one of claims 1 to 10] claim 1.

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DESCRIPTION
METHOD FOR PRODUCING CYCLIC LACTIC ACID OLIGOMER

TECHNICAL FIELD

The present invention relates to a method for producing a cyclic lactic acid oligomer, and a cyclic lactic acid oligomer produced by the production method.

BACKGROUND ART

There is known a method for producing a lactic acid oligomer by dehydration condensation reaction of lactic acids under reduced pressure. Lactic acid oligomers obtained by this method comprise both chain oligomers and cyclic oligomers.

As a method for obtaining cyclic oligomers, there is known a method which comprises, during dehydration condensation reaction of lactic acids, heating at 145°C for 3 hours under normal pressure, reducing pressure to 150mmHg, heating for 3 hours under the reduced pressure, and then heating at 185°C for 1.5 hours under a pressure of 3mmHg (Japanese Patent Application Laying-Open (kokai) No. 9-227383).

In this method, however, the generation yield of cyclic oligomers is low, and there still remains some room for improvement of the yield.

DISCLOSURE OF THE INVENTION

The object of the present invention is to provide a novel method for producing cyclic lactic acid oligomers at a high yield, and to provide a cyclic lactic acid oligomer produced by said method.

As a result of focused research to achieve the aforementioned object, the present inventors have found that a cyclic lactic acid oligomer can be produced at a high yield by dehydration condensation reaction of lactic acids under conditions of a certain pressure and a certain temperature which allow by-product water to be removed by distillation while avoiding distillation of lactides, thereby providing the present invention.

Thus, according to the present invention, there is provided a method for producing a cyclic lactic acid oligomer, which comprises:

(i) a first heating process for dehydration condensation of lactic acids by heating, which comprises dehydration condensation of lactic acids under conditions of a pressure and a temperature which allow by-product water to be removed by distillation while avoiding distillation of lactides; and

(ii) a second heating process for generating a dehydrated condensate of lactic acid, which comprises heating the reaction product from said first heating process to a temperature higher than that of the first heating process, reducing the pressure to 100mmHg or lower under conditions of a pressure and a temperature which allow by-product water to be removed by distillation while avoiding distillation of lactides, and further continuing the reaction by heating under the reduced pressure.

Preferably, in the first heating process (i), lactic acids are subjected to dehydration condensation reaction by heating to a temperature of 150°C or lower under a pressure of 10 to 760mmHg. More preferably, in the first heating process (i), lactic acids are subjected to dehydration condensation reaction by heating to a temperature ranging from 120°C to 140°C under a pressure of 350 to 400mmHg.

Preferably, in the second heating process (ii), the reaction product from the first heating process is heated to 145°C or higher, the reaction pressure is reduced to 100mmHg or lower at a depressurization rate of 0.5 to 1mmHg/min, and the reaction is further continued under the reduced pressure and at a temperature of 145°C or higher so as to generate a dehydrated condensate of lactic acid. More preferably, in the second heating process (ii), the reaction product from the first heating process is heated to 150°C to 160°C, and while the reaction pressure is reduced to 15 to 20mmHg at a depressurization rate of 0.5 to 1mmHg/min, by-product water is removed by distillation while avoiding distillation of lactides, and after the reaction pressure is reduced to 15 to 20mmHg, the reaction is further continued under the same pressure and at a reaction temperature of 150°C to 160°C so as to generate a dehydrated condensate of lactic acid

Preferably, the method for producing a cyclic lactic acid oligomer according

to the present invention further comprises:

(iii) a third heating process for generating a cyclic lactic acid oligomer, which comprises cyclization of a chain lactic acid oligomer in the reaction product from said second heating process by heating under a pressure lower than that of said second heating process.

Preferably, in the third heating process (iii), the reaction product from the second heating process is heated at 150°C to 160°C under a pressure of 0.1 to 5mmHg.

According to the particularly preferred embodiment of the present invention, there is provided a method for producing a cyclic lactic acid oligomer, which comprises:

(i) a first heating process, which comprises heating lactic acids to a temperature ranging from 120°C to 140°C under a pressure of 350 to 400mmHg for dehydration condensation reaction, while removing by-product water by distillation, and avoiding distillation of lactides;

(ii) a second heating process, which comprises heating the reaction product from said first heating process to a temperature of 150°C to 160°C, reducing the reaction pressure to 15 to 20mmHg at a depressurization rate of 0.5 to 1mmHg/min, removing by-product water by distillation while avoiding distillation of lactides, and after the reaction pressure is reduced to 15 to 20mmHg, further continuing the reaction under the same pressure and at a reaction temperature of 150°C to 160°C so as to generate a dehydrated condensate of lactic acid; and

(iii) a third heating process, which comprises cyclizing a chain lactic acid oligomer in the reaction product from said second heating process by heating at 150°C to 160°C under a pressure of 0.1 to 5mmHg so as to generate a cyclic oligomer.

In a preferred embodiment of the present invention, cyclic lactic acid oligomers are selectively produced while substantially no chain lactic acid oligomers are produced. Preferably in this case, the ratio of cyclic lactic acid oligomers to total lactic acid oligomers in the reaction product is 80% by weight or more.

According to another aspect of the present invention, there is provided a cyclic lactic acid oligomer produced by the method for producing a cyclic lactic acid

oligomer of the present invention. Preferably there is provided a cyclic lactic acid oligomer which is substantially free of chain lactic acid oligomers.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an MS spectrum of the reaction product obtained by Example 1.

Figure 2 shows a general view of NMR of the reaction product obtained by Example 1.

Figure 3 shows a partial scale view of Figure 2.

Figure 4 shows a partial scale view of Figure 2.

THE BEST MODE FOR CARRYING OUT THE INVENTION

Embodiments and methods for carrying out the present invention are described in detail below.

The method for producing a cyclic lactic acid oligomer of the present invention comprises:

(i) a first heating process for dehydration condensation of lactic acids by heating, which comprises dehydration condensation of lactic acids under conditions of a pressure and a temperature which allow by-product water to be removed by distillation while avoiding distillation of lactides; and

(ii) a second heating process for generating a dehydrated condensate of lactic acid, which comprises heating the reaction product from said first heating process to a temperature higher than that of the first heating process, reducing the pressure to 100mmHg or lower under conditions of a pressure and a temperature which allow by-product water to be removed by distillation while avoiding distillation of lactides, and further continuing the reaction by heating under the reduced pressure.

The lactic acid used as a raw material in the present invention may be any one of D-lactic acid, L-lactic acid and DL-lactic acid, and these lactic acids may also be used alone or in combination of two or more.

The first heating process in the present invention is a process of dehydration condensation of lactic acids by heating under conditions of a pressure and a temperature which allow by-product water to be removed by distillation while avoiding distillation of lactides. In the reaction of the first heating process, by-product water generated by dehydration condensation of lactic acids is removed by distillation in order to achieve smooth progression of the reaction, and in this case, a pressure and a temperature are determined so as to avoid distillation of lactide that is a dehydrated condensate of 2 molecules of lactic acid.

The reaction pressure may be normal pressure or reduced pressure, and reduced pressure is preferable. The reaction pressure is specifically 10 to 760mmHg, preferably 300 to 500mmHg, and more preferably 350 to 400mmHg. The reaction temperature depends on pressure conditions, but generally is within a range of 100°C to 150°C, preferably 120°C to 140°C.

The reaction period of the first heating process is not particularly limited, but is generally 3 to 12 hours, preferably 5 to 6 hours.

A reaction product containing, as a main component, a dehydrated condensate of 3 to 23 molecules of lactic acid, is generated from the reaction of the first heating process.

According to the method of the present invention, after completion of the first heating process mentioned above, in the second heating process, the reaction product is heated to a temperature higher than the reaction temperature of the first heating process, e.g. 145°C or higher, preferably 150°C to 180°C, more preferably 150°C to 160°C so as to obtain oligomers having a higher average polymerization degree, and at the same time the reaction pressure is reduced to 100mmHg or lower, preferably 10 to 80mmHg, more preferably 15 to 20mmHg, and then dehydration condensation reaction is further continued.

As in the case of the reaction of the first heating process, the reaction of the second heating process is carried out under conditions such that allow by-product water to be removed by distillation, but distillation of lactides is avoided, so as to smoothly

progress the reaction.

From the studies of the present inventors, it was found that a rate of reducing reaction pressure (depressurization rate) within the above-stated range (i.e. 100mmHg or lower) should be maintained at no higher than 5mmHg/min in order to avoid distillation of lactides and to increase reaction efficiency. The depressurization rate is preferably in a range from no lower than 0.25mmHg/min to no higher than 5mmHg/min, more preferably from no lower than 0.25mmHg/min to no higher than 4mmHg/min, still more preferably from no lower than 0.5mmHg/min to no higher than 3mmHg/min, and particularly preferably from no lower than 0.5mmHg/min to no higher than 1mmHg/min. A depressurization rate lower than the range stated above is not preferable since time required for reducing the pressure to a designated pressure is longer, and a depressurization rate of 5mmHg/min or higher is not preferable since lactides are removed by distillation with by-product water.

After the reaction pressure is reduced to 100mmHg or lower, the reaction is further continued at this reaction pressure. The reaction period of this case is 3 to 12 hours, preferably 5 to 6 hours.

There is obtained from the reaction of the second heating process, a lactic acid oligomer having an average polymerization degree of 3 to 30, preferably 3 to 23. The ratio of cyclic lactic acid oligomers to total lactic acid oligomers in the reaction product from the second heating process is generally 70% by weight or more, and for example, around 70% to 80% by weight.

In a preferred embodiment of the present invention, a third heating process is carried out after completion of the aforementioned second heating process. The third heating process is a process where a chain lactic acid oligomer in the reaction product from the second heating process is cyclized by heating at a pressure still lower than that of the second heating process so as to generate a cyclic lactic acid oligomer.

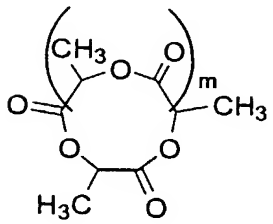
The reaction pressure of the third heating process is preferably 0.1 to 5mmHg, more preferably 0.25 to 5mmHg, still more preferably 0.5 to 3mmHg, and particularly preferably 0.5 to 1mmHg. The reaction temperature of the third heating process is

preferably 145°C to 180°C, and more preferably 150°C to 160°C.

The reaction is continuously performed under such pressure and temperature conditions. The reaction period is 3 to 12 hours, preferably 5 to 6 hours. By-product water generated in this case is also removed by distillation. In this case, it is preferable to avoid distillation of lactides, but it is not necessary to set the depressurization rate especially low since almost no lactides are contained in the reaction product.

The reaction of the third heating process generates a cyclic lactic acid oligomer having an average polymerization degree of 3 to 30, preferably 3 to 23. The ratio of cyclic lactic acid oligomers to total lactic acid oligomers in the reaction product from the third heating process is generally 90% by weight or more, and preferably 99% by weight or more.

The cyclic lactic acid oligomer produced by the method of the present invention is assumed to have the following chemical structure:



(1)

wherein m is an integer of 1 to 28, and preferably m is an integer of 1 to 19.

In a preferred embodiment of the method for producing a cyclic lactic acid oligomer of the present invention, cyclic lactic acid oligomers can selectively be produced while substantially no chain lactic acid oligomers are produced. The term "substantially no chain lactic acid oligomers are produced" is used herein to mean that the ratio of cyclic lactic acid oligomers to total lactic acid oligomers in a reaction product is 80% by weight or more, preferably 90% by weight or more, more preferably 95% by weight or more, and particularly preferably 99% by weight or more.

The present invention also relates to a cyclic lactic acid oligomer produced by the aforementioned method for producing a cyclic lactic acid of the present invention.

In a preferred embodiment of the present invention, a mixture of cyclic lactic acid oligomers substantially free of chain lactic acid oligomers can be produced. The term "a mixture of cyclic lactic acid oligomers substantially free of chain lactic acid oligomers" is used herein to mean that the ratio of cyclic lactic acid oligomers to total lactic acid oligomers in the mixture is 80% by weight or more, preferably 90% by weight or more, more preferably 95% by weight or more, and particularly preferably 99% by weight or more.

The mixture of cyclic lactic acid oligomers produced by the method of the present invention (or a single substance obtained by purification from the mixture) is useful as a tumor cell growth inhibiting agent, an antineoplastic agent, a preventive agent against cancer metastasis, a QOL improving agent for cancer patients, an immune activating agent, and the like, and the mixture can also be used for prevention and/or treatment of diabetes or diabetes complications since it has an action of reducing blood sugar level. Moreover, the mixture of cyclic lactic acid oligomers produced by the method of the present invention (or a single substance obtained by purification from the mixture) has an action of repressing excessive appetite and promoting basal metabolism, and so it can be used also as a medicament useful for improvement and/or prevention of adiposis and enhancement of effects of kinesitherapy, and is also useful as an agent for promoting glycogen accumulation or an agent for enhancing physical fitness. Furthermore, a cyclic lactic acid oligomer produced by the method of the present invention is useful not only as a medicament, but also as health foods or diet supplements including beverages, which is generally called soft drinks, drinkable preparations, health foods, specific hygienic foods, functional foods, function activating foods, nutritional supplementary foods, supplements, feed, feed additives, and the like.

The present invention is further described in the following examples. It is apparent to those skilled in the art that materials, usage, proportion, treatment, treatment process and the like shown in the following examples can be modified as appropriate, as long as the modifications are within the spirit and scope of the invention, and the examples are not intended to limit the scope of the invention.

EXAMPLES

Example 1.

10.0g of (s)-(+)-lactic acid was placed in a 100ml (internal volume) eggplant-shaped flask, which was then set on a rotary evaporator. The pressure in the flask was controlled to be 350 to 400mmHg, and the flask was heated to 140°C, followed by reaction at the same pressure and the same temperature for 6 hours (the first heating process). By-product water generated from this reaction was removed by distillation. Almost no lactides were removed by distillation outside the system under the above reaction conditions.

Then, the reaction temperature was raised to 150 to 160°C, and the reaction pressure was gradually reduced from 400mmHg to 15 to 20mmHg over about 6 hours (depressurization rate: 1mmHg/min). At this depressurization rate, by-product water was removed by distillation, but almost no lactides were removed by distillation. After that, the pressure was maintained at 15 to 20mmHg and the reaction was continuously performed for 6 hours (the second heating process).

Subsequently, the pressure was reduced to 1 to 3mmHg over 30 minutes, and then the reaction was continuously performed at a reaction temperature of 160°C for 5 hours (the third heating process).

After completion of the reaction, the reaction product was analyzed and as a result, there was obtained 6.80g (yield 85%) of cyclic oligomer having an average polymerization degree of 3 to 21.

An MS spectrum of the reaction product obtained in Example 1 is shown in Figure 1. A general view of NMR of the reaction product obtained in Example 1 is shown in Figure 2, and partial scale views of Figure 2 are shown in Figures 3 and 4.

Example 2.

10.0g of (s)-(+)-lactic acid was placed in a 100ml (internal volume) eggplant-shaped flask, which was then set on a rotary evaporator. The pressure in the

flask was controlled to be 760mmHg, and the flask was heated to 140°C, followed by reaction at the same pressure and the same temperature for 10 hours (the first heating process). By-product water generated from this reaction was removed by distillation. Almost no lactides were removed by distillation outside the system under the above reaction conditions.

Then, the reaction temperature was raised to 150 to 160°C, and the reaction pressure was gradually reduced from 760mmHg to 15 to 20mmHg over about 12 hours (depressurization rate: 1mmHg/min). At this depressurization rate, by-product water was removed by distillation, but almost no lactides were removed by distillation. After that, the pressure was maintained at 15 to 20mmHg and the reaction was continuously performed for 6 hours (the second heating process).

Subsequently, the pressure was reduced to 1 to 3mmHg over 30 minutes, and then the reaction was continuously performed at a reaction temperature of 160°C for 5 hours (the third heating process).

After completion of the reaction, the reaction product was analyzed and as a result, there was obtained 6.80g (yield 85%) of cyclic oligomer having an average polymerization degree of 3 to 21.

An MS spectrum and NMR of the reaction product obtained in Example 2 were the same as those of the reaction product obtained in Example 1.

Example 3.

10.0g of (s)-(+)-lactic acid was placed in a 100ml (internal volume) eggplant-shaped flask, which was then set on a rotary evaporator. The pressure in the flask was controlled to be 350 to 400mmHg, and the flask was heated to 140°C, followed by reaction at the same pressure and the same temperature for 6 hours (the first heating process). By-product water generated from this reaction was removed by distillation. Almost no lactides were removed by distillation outside the system under the above reaction conditions.

Then, the reaction temperature was raised to 150 to 160°C, and the reaction

pressure was gradually reduced from 400mmHg to 70mmHg over about 5.5 hours (depressurization rate: 1mmHg/min). At this depressurization rate, by-product water was removed by distillation, but almost no lactides were removed by distillation. After that, the pressure was maintained at 70mmHg and the reaction was continuously performed for 10 hours (the second heating process).

Subsequently, the pressure was reduced to 1 to 3mmHg over 70 minutes, and then the reaction was continuously performed at a reaction temperature of 160°C for 5 hours (the third heating process).

After completion of the reaction, the reaction product was analyzed and as a result, there was obtained 6.80g (yield 85%) of cyclic oligomer having an average polymerization degree of 3 to 21.

An MS spectrum and NMR of the reaction product obtained in Example 3 were the same as those of the reaction product obtained in Example 1.

Comparison Example 1.

Comparison Example 1 was carried out in the same manner as in Example 1 with the exception that depressurization rate in the second heating process was set to be 5mmHg/min. In the depressurization operation, lactides were removed by distillation with by-product water, and as a result, the yield of cyclic oligomer was decreased to 60%.

INDUSTRIAL APPLICABILITY

According to the present invention, a cyclic lactic acid oligomer having an average polymerization degree of 3 to 30, preferably 3 to 21, can be produced at a high yield from lactic acids without using a catalyst. Moreover, a cyclic lactic acid oligomer produced by the production method of the present invention is useful as a tumor cell growth inhibiting agent, antineoplastic agent, preventive agent against cancer metastasis, QOL improving agent for cancer patients, immune activating agent, therapeutic agent for diabetes, antiobestic agent, a agent for promoting glycogen

accumulation or an agent for enhancing physical fitness. Furthermore, the cyclic lactic acid oligomer is useful not only as a medicament, but also as various types of health foods and diet supplements including soft drinks, drinkable preparations, health foods, specific hygienic foods, functional foods, function activating foods, nutritional supplementary foods, supplements, feed, feed additives, and the like.

CLAIMS

1. A method for producing a cyclic lactic acid oligomer, which comprises:
(i) a first heating process for dehydration condensation of lactic acids by heating, which comprises dehydration condensation of lactic acids under conditions of a pressure and a temperature which allow by-product water to be removed by distillation while avoiding distillation of lactides; and
(ii) a second heating process for generating a dehydrated condensate of lactic acid, which comprises heating the reaction product from said first heating process to a temperature higher than that of the first heating process, reducing the pressure to 100mmHg or lower under conditions of a pressure and a temperature which allow by-product water to be removed by distillation while avoiding distillation of lactides, and further continuing the reaction by heating under the reduced pressure.

2. The method for producing a cyclic lactic acid oligomer according to claim 1, wherein in the first heating process (i), lactic acids are subjected to dehydration condensation reaction by heating to a temperature of 150°C or lower under a pressure of 10 to 760mmHg.

3. The method for producing a cyclic lactic acid oligomer according to claim 1 or 2, wherein in the first heating process (i), lactic acids are subjected to dehydration condensation reaction by heating to a temperature ranging from 120°C to 140°C under a pressure of 350 to 400mmHg.

4. The method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 3, wherein in the second heating process (ii), the reaction product from the first heating process is heated to 145°C or higher, the reaction pressure is reduced to 100mmHg or lower at a depressurization rate of 0.5 to 1mmHg/min, and the reaction is further continued under the reduced pressure and at a temperature of 145°C or higher so as to generate a dehydrated condensate of lactic acid.

5. The method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 4, wherein in the second heating process (ii), the reaction product from the first heating process is heated to 150°C to 160°C, and while the reaction pressure is reduced to 15 to 20mmHg at a depressurization rate of 0.5 to 1mmHg/min, by-product water is removed by distillation while avoiding distillation of lactides, and after the reaction pressure is reduced to 15 to 20mmHg, the reaction is further continued under the same pressure and at a reaction temperature of 150°C to 160°C so as to generate a dehydrated condensate of lactic acid.

6. The method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 5, which further comprises:

(iii) a third heating process for generating a cyclic lactic acid oligomer, which comprises cyclization of a chain lactic acid oligomer in the reaction product from said second heating process by heating under a pressure lower than that of said second heating process.

7. The method for producing a cyclic lactic acid oligomer according to claim 6, wherein in the third heating process (iii), the reaction product from the second heating process is heated at 150°C to 160°C under a pressure of 0.1 to 5mmHg.

8. The method for producing a cyclic lactic acid oligomer according to claim 1, which comprises:

(i) a first heating process, which comprises heating lactic acids to a temperature ranging from 120°C to 140°C under a pressure of 350 to 400mmHg for dehydration condensation reaction, while removing by-product water by distillation, and avoiding distillation of lactides;

(ii) a second heating process, which comprises heating the reaction product from said first heating process to a temperature of 150°C to 160°C, reducing the reaction pressure

to 15 to 20mmHg at a depressurization rate of 0.5 to 1mmHg/min, removing by-product water by distillation while avoiding distillation of lactides, and after the reaction pressure is reduced to 15 to 20mmHg, further continuing the reaction under the same pressure and at a reaction temperature of 150°C to 160°C so as to generate a dehydrated condensate of lactic acid; and

(iii) a third heating process, which comprises cyclizing a chain lactic acid oligomer in the reaction product from said second heating process by heating at 150°C to 160°C under a pressure of 0.1 to 5mmHg so as to generate a cyclic oligomer.

9. The method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 8, wherein cyclic lactic acid oligomers are selectively produced while substantially no chain lactic acid oligomers are produced.

10. The method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 9, wherein the ratio of cyclic lactic acid oligomers to total lactic acid oligomers in the reaction product is 80% by weight or more.

11. A cyclic lactic acid oligomer produced by the method for producing a cyclic lactic acid oligomer according to any one of claims 1 to 10.

12. The cyclic lactic acid oligomer according to claim 11, which is substantially free of chain lactic acid oligomers.

ABSTRACT

The object of the present invention is to provide a novel method for producing cyclic lactic acid oligomers at a high yield, and to provide a cyclic lactic acid oligomer produced by said method. According to the present invention, there is provided a method for producing a cyclic lactic acid oligomer, which comprises:

(i) a first heating process for dehydration condensation of lactic acids by heating, which comprises dehydration condensation of lactic acids under conditions of a pressure and a temperature which allow by-product water to be removed by distillation while avoiding distillation of lactides; and

(ii) a second heating process for generating a dehydrated condensate of lactic acid, which comprises heating the reaction product from said first heating process to a temperature higher than that of the first heating process, reducing the pressure to 100mmHg or lower under conditions of a pressure and a temperature which allow by-product water to be removed by distillation while avoiding distillation of lactides, and further continuing the reaction by heating under the reduced pressure; as well as a cyclic lactic acid oligomer produced by said production method.

(特許協力条約に基づいて公開された国際出願)

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[続葉有]

(54) Title: PROCESS FOR THE PREPARATION OF CYCLIC LACTIC ACID OLIGOMERS

(54) 発明の名称: 環状乳酸オリゴマーの製造方法

(57) Abstract: A process for the preparation of cyclic lactic acid oligomers, which comprises (i) the first heating step of condensing lactic acid through dehydration by heating under such conditions of pressure and temperature that by-product water can be distilled away while avoiding the distillation-off of lactide, and (ii) the second heating step of lowering the pressure of the resulting reaction system to 100mmHg or below at a temperature higher than that of the first step under such conditions of pressure and temperature that by-product water can be distilled away while avoiding the distillation-off of lactide, and further continuing the reaction under the resulting lowered pressure by heating to form a condensate of lactic acid; and cyclic lactic acid oligomers prepared by the process.

(57) 要約:

本発明によれば、(i)乳酸を加熱により脱水縮合する工程であって、ラクチドの留出を回避しつつ副生水を留出除去するような圧力及び温度条件下で脱水縮合する第1加熱工程;及び
(ii)該第1加熱工程の反応生成物を、第1加熱工程より高い温度において、ラクチドの留出を回避しつつ副生水を留出除去するような圧力及び温度条件下で圧力を10ommHg以下まで降下させ、該降下した圧力において加熱下においてさらに反応を継続して乳酸の脱水縮合物を生成させる第2加熱工程、
を含む環状乳酸オリゴマーの製造方法、並びに該製造方法により製造される環状乳酸オリゴマーが提供される。

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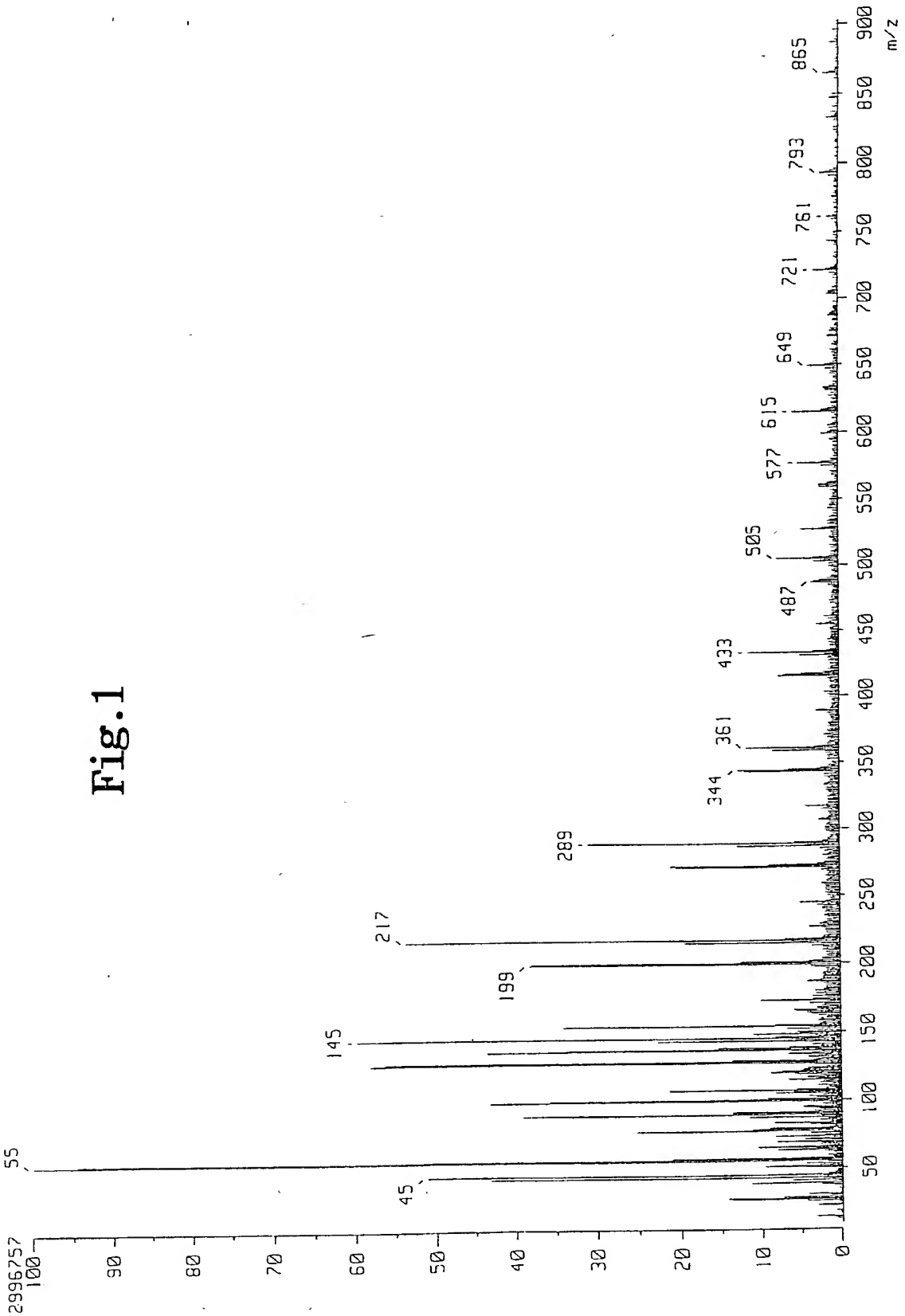
Fig.1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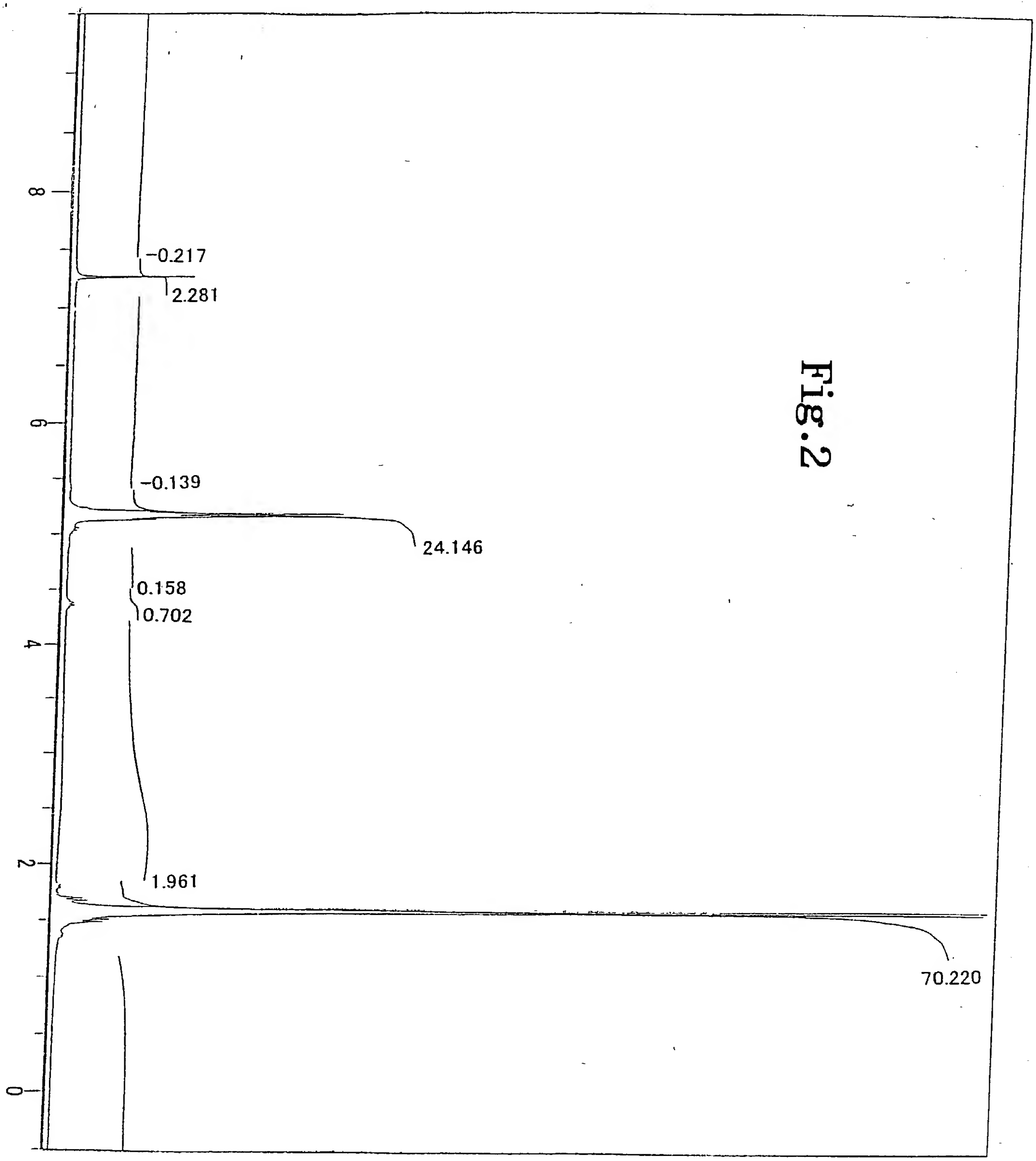

Fig.2

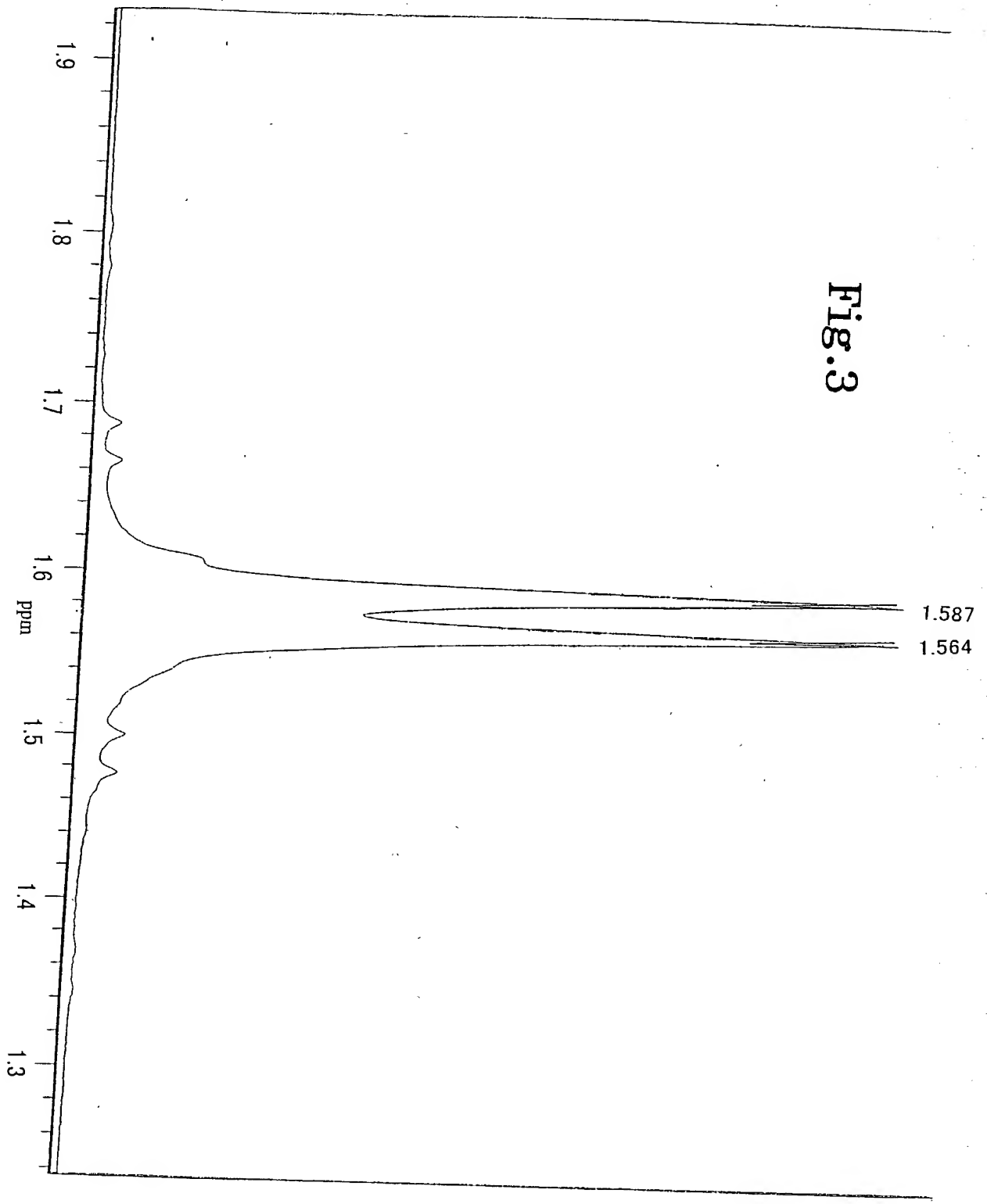

Fig.3

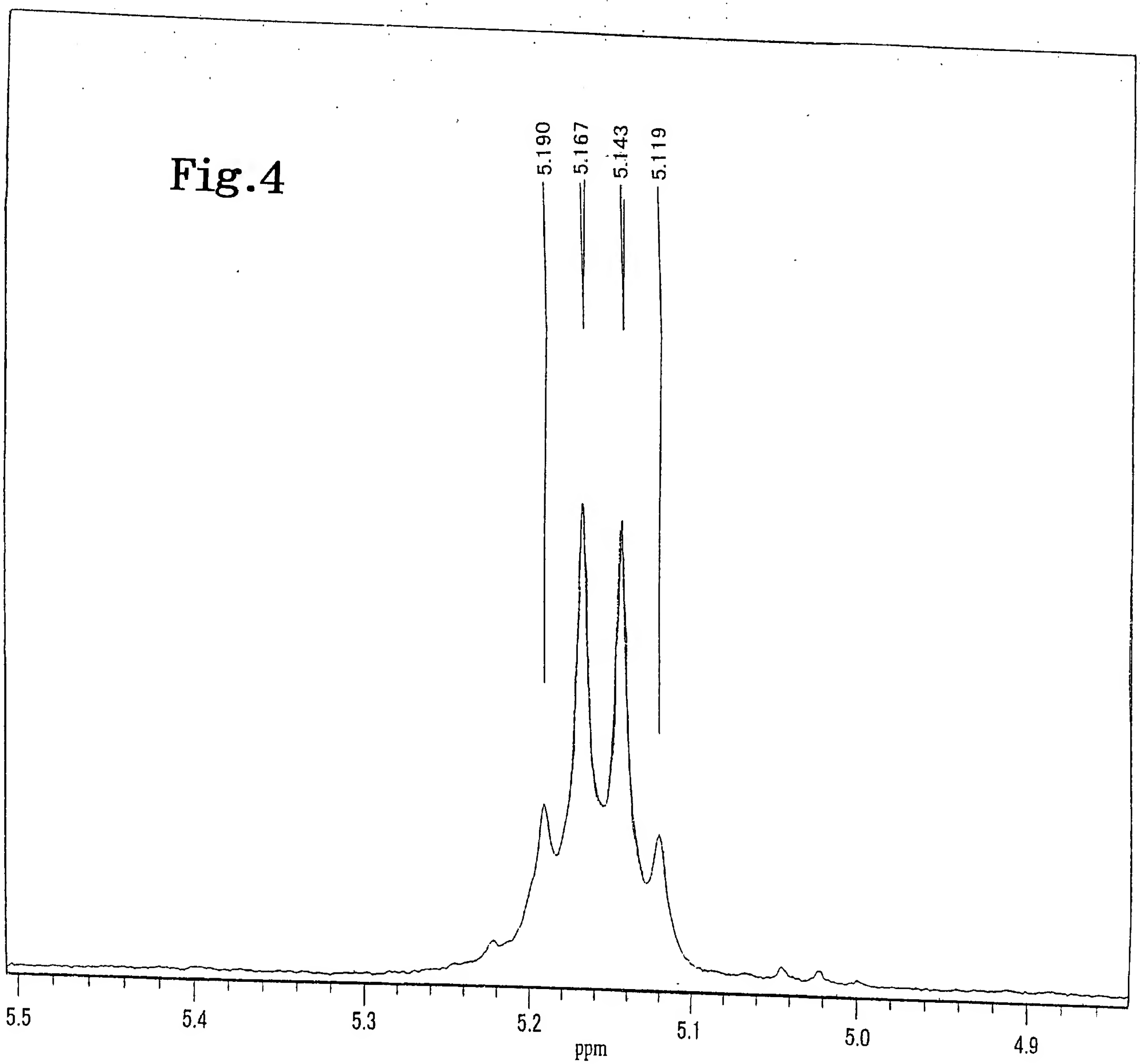

Fig.4

FA1556A/US

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25 JUN 2002

Declaration and Power of Attorney for Utility or Design Patent Application
特許出願宣言書

10/070435

Japanese Language Declaration

私は、下欄に氏名を記載した発明者として、以下のとおり宣言する：

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As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Method for Producing Cyclic Lactic Acid Oligomer

上記発明の明細書（下記の欄で x 印がついていない場合は、本書に添付）は、

☐ ____年____月____日に提出され、米国出願番号
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____年____月____日に訂正されました。又は、

特許協定条約国際出願番号_____とし、
（該当する場合）____年____月____日に訂正されました。

the specification of which is attached hereto unless the following box is checked:

☒ was filed on **20/Sep/00** as United States Application Number **10/070435** and was amended on **19/Mar/02** (if applicable) or,

PCT International Application Number **PCT/JP00/06399** and was amended on _____ (if applicable).

私は、前記のとおり補正した請求の範囲を含む前記明細書の内容を検討し、理解したことを陳述する。

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

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I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

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I hereby claim foreign priority under Title 35, United States Code §119(a-d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States, listed below. I have also identified below, by checking the "No" box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed:

Prior foreign applications 先の外国出願			Priority claimed 優先権の主張
11-265732 (Number) （番号）	**Japan** (Country) (国名)	**20/Sep/99** (Day/Month/Year Filed) (出願の年月日)	☒ Yes ☐ No あり なし
_____ (Number) （番号）	_____ (Country) (国名)	_____ (Day/Month/Year Filed) (出願の年月日)	☐ Yes ☐ No あり なし

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☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto.

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私は、合衆国法典第 35 部第 119 条(e)項に基づく、下記の合衆国仮特許出願の利益を主張する。

I hereby claim the benefit under Title 35, United States Code §119 (e) of any United States provisional application(s) listed below.

(Application No) (出願番号)	(Day/Month/Year Filed) (出願の年月日)
(Application No.) (出願番号)	(Day/Month/Year Filed) (出願の年月日)
(Application No) (出願番号)	(Day/Month/Year Filed) (出願の年月日)

☐ その他の合衆国仮特許出願番号は別紙の追補優先権欄にて記載する。

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I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Application No.) (出願番号)	(Day/Month/Year Filed) (出願の年月日)	(現況) (特許済み、係属中 放棄済み) (Status) (patented, pending, abandoned)
(Application No.) (出願番号)	(Day/Month/Year Filed) (出願の年月日)	(現況) (特許済み、係属中 放棄済み) (Status) (patented, pending, abandoned)

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(Supply similar information and signature for third and subsequent joint inventors.)

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共同発明者の署名　日付	Fourth Inventor's signature　Date Masahiro Murakami　June 10, 2002
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第五の共同発明者の氏名（該当する場合）	Full name of fifth joint inventor, if any
共同発明者の署名　日付	Fifth Inventor's signature　Date
住所	Residence
国籍	Citizenship
郵便の宛先	Post Office Address
第六の共同発明者の氏名（該当する場合）	Full name of sixth joint inventor, if any
共同発明者の署名　日付	Sixth Inventor's signature　Date
住所	Residence
国籍	Citizenship
郵便の宛先	Post Office Address

（それ以降の共同発明者に対しても同様な情報および署名を提供すること。）

(Supply similar information and signature for subsequent joint inventors.)